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CURRENT ETS DEVELOPMENTS REPORT

August 23, 2002

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CURRENT ETS DEVELOPMENTS REPORT

IN THE UNITED STATES

STATE AND LOCAL GOVERNMENTS

REGION 10 – WESTERN
AZ, CO, MT, ND, NM, SD, UT, WY

[1] Colorado City Prohibits Indoor and Outdoor Smoking

Louisville, Colorado, smokers may apparently be unable to smoke anywhere but in their own homes under a new ordinance that takes effect October 8, 2002. While the law reportedly prohibits smoking indoors and outdoors at restaurants, bars and private clubs, council members were unclear as to whether it would also be applied to other outdoor public areas, such as bus stops, ball fields and street concerts. According to a news source, council members decided to let the details be worked out after the law takes effect. Louisville apparently becomes the second city in the county enforcing such a strict ordinance, and Boulder County Health Department director Chuck Stout was quoted as saying, "I believe by the time we reach the end of this decade, this will be a smoke-free county." Tavern owners and bartenders are reportedly concerned about loss of business in those establishments where most patrons are smokers. *See Bouldernews.com*, August 21, 2002.

ETS-RELATED LITIGATION AGAINST CIGARETTE MANUFACTURERS

[2] *Flight Attendant Litigation*: Trial Underway in *Janoff*

Jury selection in the *Suzette Janoff* case has been completed, and opening statements were expected to begin during the afternoon of August 23, 2002.

On August 15, Judge Leslie Rothenberg indicated she would follow Judge Robert Kaye's October 2000 order that shifted the burden of proof from plaintiffs to defendants on the issue of general causation for five enumerated diseases and created a "rebuttable presumption" of general causation. The latter finding, according to Judge Kaye, eliminated the need for each plaintiff to prove the essential elements of strict liability in tort, negligence and breach of implied warranty. Judge Kaye's order limits the issues to be tried to specific causation and damages.

Janoff, age 45, alleges chronic sinusitis, vasomotor rhinitis and asthma as a result of exposure to ETS while employed as a flight attendant by American Airlines. From 1983-1990, she flew domestic routes for the carrier but switched to international routes in 1990. In April 1988, the U.S. government prohibited smoking on domestic flights two hours or shorter in duration; in February 1990, the U.S. government prohibited smoking on all domestic flights six hours or shorter in duration. Plaintiff quit working for American Airlines in March 1996.

Janoff is represented by the Angones, Hunter and Grover, Weinstein firms of Miami. *Janoff v. Philip Morris Incorporated, et al.* (Circuit Court, Miami-Dade County, Florida) (filed February 2, 2000)

[3] *Myers*: Deadline for Seeking Rehearing with California Supreme Court Expires

To our knowledge, plaintiffs did not seek rehearing of the California Supreme Court's August 5, 2002, rulings in the *Myers* and *Naegele* cases by the August 20 deadline; the tobacco companies chose not to seek rehearing. The August 5 rulings addressed the effect of an amendment repealing the immunity cigarette manufacturers previously enjoyed under California product liability law.

California Supreme Court decisions normally become final 30 days from issuance, unless one of the parties moves for reconsideration or the court extends the period on its own motion. Several cases pending before both the California Supreme Court and the U.S. Court of Appeals

for the Ninth Circuit have been stayed pending resolution of the appeal.

Betty Jean Myers, a long-time smoker, alleges that she developed lung cancer from ETS exposure, not active smoking. On October 5, 1999, the trial court granted defendants' motion to dismiss the case based on the application of California product liability statutes to plaintiff's claims. The court then entered final judgment in defendants' favor. Plaintiff appealed the ruling to the Ninth Circuit Court of Appeals, which then certified questions of California law to the Supreme Court. Plaintiff in *Naegele* did not assert any ETS claims.

Myers claims to have smoked Viceroy, Winston and Virginia Slims cigarettes between 1956 and 1997. She also contends that she has "worked in and owned a variety of businesses in which it was the custom for patrons to congregate and smoke heavily," though she does not identify those businesses in her complaint. She alleges that her lung cancer was diagnosed on April 8, 1998, and that it was caused by ETS exposure only.

Defendants named in Myers' complaint are Philip Morris, R.J. Reynolds, Brown & Williamson, and Does. Myers is represented by the Visalia, California, firm of Bourdette & Partners. Myers states in her complaint that she resides in Arkansas, though her ETS exposure occurred in Tulare County, California. Myers *v.* Philip Morris, *Inc.*, et al(U.S. District Court, Eastern District, California; on appeal to the U.S. Court of Appeals, Ninth Circuit; question certified to the California Supreme Court) (filed March 4, 1999).

ETS CASES NOT INVOLVING CIGARETTE MANUFACTURERS

PUBLIC PLACE EXPOSURE: SMOKING LAWS AND ORDINANCES

[4] ***Hall Drive Ins, Inc. v. Fort Wayne*, 2002 WL 1897895 (Supreme Court of Indiana) (decided August 16, 2002)**

The Indiana Supreme Court has upheld a citation against a restaurant that was charged with violating the City of Fort Wayne Smoking Ordinance. The restaurant owner had argued that because the bar section of the facility was not open to children younger than age 18, it was exempt from the smoking ordinance and was not required to enclose the bar area or prohibit smoking there. In rejecting this interpretation of the ordinance, the court noted that it would "be contrary to the express purpose of the ordinance to reduce the exposure of children to second-hand smoke," particularly where, as here, children were permitted in the restaurant area adjacent to the bar. In its opinion, the court recites the statutory findings, i.e., that children are among those "at special risk to secondhand smoke."

SCIENTIFIC/TECHNICAL ITEMS

RESPIRATORY DISEASES AND CONDITIONS – ADULTS

Non-ETS Asthma Literature

[5] **"Candidate Genes for Atopic Asthma: Current Results from Genome Screens," E. Noguchi, and T. Arinami, *American Journal of Pharmacogenomics* 1(4): 251-261, 2001 [See Appendix A]**

According to the authors of this review paper, the evidence linking asthma with various candidate genes is only suggestive. They speculate that new technology and data from the Human Genome Project should allow researchers to more completely examine the genetic component of this complex disorder.

[6] **"Obesity Is a Risk Factor for Dyspnea but Not for Airflow Obstruction," D.D. Sin, R.L. Jones, and S.F.P. Man, *Archives of Internal Medicine* 162: 1477-1481, 2002 [See Appendix A]**

Data from this study demonstrate that while obesity is a risk factor for self-reported asthma and increased bronchodilator use, it is associated with a decreased risk of airflow obstruction, generally used as a defining characteristic of asthma.

[7] **"Viral Induction of a Chronic Asthma Phenotype and Genetic Segregation from the Acute Response," M.J. Walter, J.D. Morton, N. Kajiwara, E. Agapov, and M.J. Holtzman, *The Journal of Clinical Investigation* 110(2): 165-175, 2002 [See Appendix A]**

These authors report finding that a single viral infection in mice has the capacity to produce permanent changes in airway behavior, similar to those found in asthma.

RESPIRATORY DISEASES AND CONDITIONS – CHILDREN

[8] **"Identification of Population Subgroups of Children and Adolescents with High Asthma Prevalence: Findings from the Third National Health and Nutrition Examination Survey," M.A. Rodriguez, M.A. Winkleby, D. Ahn, and J. Sundquist, *Archives of Pediatric and Adolescent Medicine* 156(3): 269-275, 2002 [See Appendix A]**

Children with a parental history of asthma or hay fever are four times as likely to report current asthma, according to these authors. Further, obese children are reported to be almost twice as likely to have asthma. The authors were unable to find an association between asthma and ETS exposure.

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[9] **"Environmental Toxins and Breast Cancer on Long Island. I. Polycyclic Aromatic Hydrocarbon DNA Adducts," M.D. Gammon, R.M. Santella, A.L. Neugut, S.M. Eng, S.L. Teitelbaum, A. Paykin, B. Levin, M.B. Terry, T.L. Young, L.W. Wang, Q. Wang, J.A. Britton, M.S. Wolff, S.D. Stellman, M. Hatch, G.C. Kabat, R. Senie, G. Garbowski, C. Maffeo, P. Montalvan, G. Berkowitz, M. Kemeny, M. Citron, F. Schnabel, A. Schuss, S. Hajdu, and V. Vinceguerra, *Cancer Epidemiology, Biomarkers & Prevention* 11: 677-685, 2002 [See Appendix A]**

These authors report a 50-percent increased risk of breast cancer associated with polycyclic aromatic hydrocarbon (PAH) DNA adducts. They observed no relationship between PAH-DNA adduct level and major sources of PAH, including ETS exposure.

ETS EXPOSURE AND MONITORING

[10] **"Prevalence of Exposure to Environmental Tobacco Smoke at Work and at Home – 15-year Trends in Finland," P. Jousilahti, and S. Helakorpi, *Scandinavian Journal of Work, Environment & Health* 28(2): 16-20, 2002 [See Appendix A]**

These authors estimate that in the Finnish population 14 percent of nonsmokers ages 15 to 64 years are exposed to ETS, either at home or in the workplace. They describe marked decreases in ETS exposure over the past 15 years, attributing these decreases to both legislation prohibiting smoking in public places and a general decrease in smoking rates.

[11] **"Exposure to Environmental Tobacco Smoke in Finland in 2000," T.P. Kauppinen, and S.V. Virtanen, *Scandinavian Journal of Work, Environment & Health* 28(2): 7-15, 2002 [See Appendix A]**

Estimates of both ETS and nicotine exposure among the Finnish population are provided by the authors of this paper. They note that despite legal restrictions on smoking, ETS exposure is "still probably the most frequent occupational exposure to a chemical carcinogen."

APPENDIX A

The numbers assigned to the following article summaries correspond with the numbers assigned to the synopses of the articles in the text of this Report.

RESPIRATORY DISEASES AND CONDITIONS – ADULTS

Non-ETS Asthma Literature

[5] "Candidate Genes for Atopic Asthma: Current Results from Genome Screens," E. Noguchi, and T. Arinami, *American Journal of Pharmacogenomics* 1(4): 251-261, 2001

"Atopic diseases such as asthma, atopic dermatitis, and allergic rhinitis are major causes of morbidity in developed countries and have been increasing in incidence. Familial aggregation of asthma was first observed by Sennertus in 1650, ... Although numerous subsequent family studies confirmed a genetic component for asthma and atopy, the precise mode of inheritance for asthma has not yet been determined. Several modes of inheritance including a single dominant gene with partial penetrance and a single recessive gene with partial penetrance have been suggested. However, it is unlikely that a single gene is responsible for development of the diseases; instead, atopy is likely to be a polygenic disorder resulting from the interaction of multiple genes."

"The increase in the incidence of allergic disease in the last 20 years is too rapid to be explained by changes in the gene pool, suggesting the importance of environmental factors, such as allergen exposure and infection, for the development of allergic diseases.... Infection also seems to play a role in the development of allergic diseases. Epidemiologic studies show an inverse relationship between atopy and infectious diseases, which suggests that exposure to infectious pathogens such as *Mycobacterium tuberculosis* may reduce the risk for allergic disease. Collectively, asthma appears to be a multifactorial polygenic disorder in which several genes and environmental factors play roles."

"There are 2 approaches to identifying the disease susceptibility genes in atopic asthma. The first is to focus on functional candidate genes, such as the cytokine cluster, receptors, recognition molecules, and transcription factors that play important roles in allergic inflammation and IgE production. This approach is quite useful and has led to identification of variants that might confer asthma susceptibility. However, unknown genes that actually attribute to the development of asthma will not be identified in this approach. The second approach is to screen for linkage across the entire genome with highly polymorphic DNA markers positioned at specific intervals along each chromosome. A genome-wide linkage screen is costly and very labor-intensive, but with the aid of recent technical advances and data from the Human Genome Project, genome-wide approaches have been used by several groups to identify loci linked to asthma. Genes and predicted genes located in regions of linkage can be explored to identify disease-associated genes. In addition, a genome-wide association approach using single nucleotide polymorphisms (SNPs) has been undertaken."

"In this review, we concentrate on the potential candidate genes for childhood asthma that are localized to 7 chromosome regions. The regions and candidate genes presented here are a personal selection and do not claim to be complete."

"Although many interesting candidate genes have been proposed to play a role in asthma, none have been established with strengths comparable with those of the susceptibility genes for breast cancer, Alzheimer's disease or celiac disease. In the genome scans, the identified regions have been large and each may include tens to hundreds of genes that are unknown. Selecting candidate genes for such a complex disorder as asthma from so many genes on a functional basis is very difficult and might be misleading. Asthma and allergy genetics have left the level of assembling mere lists of candidate genes and linked regions and have entered a field of practical implications with regard to functional analysis of Th2 type immune response and pharmacogenetics."

"To identify gene-gene interactions in such a complex disease, it is necessary to examine hundreds of thousands of genetic variants simultaneously. Subsequent to recent advances in technology and the Human Genome Project, a group in Japan (RIKEN) has undertaken genome-wide SNP searches for complex disease, including asthma, in the Japanese. In addition, the Whitehead Institute for Biomedical Research is beginning a genome-wide SNP screen of American and European populations. Findings from these studies will clarify the mechanisms underly-

ing the development of asthma and may lead to improved genetic testing and development of new drugs."

[6] **"Obesity Is a Risk Factor for Dyspnea but Not for Airflow Obstruction," D.D. Sin, R.L. Jones, and S.F.P. Man, *Archives of Internal Medicine* 162: 1477-1481, 2002**

"We used data from the Third National Health and Nutrition Examination Survey (NHANES III) to determine whether obesity is an important risk factor for OAD [obstructive airway disease] (using spirometric information), self-reported asthma, and use of bronchodilators. Specifically, we wanted to test the hypothesis that obesity is associated with increased prevalence of self-reported asthma and increased prevalence of airflow obstruction."

"Using population-based data from the NHANES III questionnaire, we found that the point prevalence of self-reported asthma was higher in obese than in nonobese participants. Use of bronchodilators was likewise highest among the obese. Paradoxically, however, there was a lower prevalence of significant airflow obstruction in the high than in the low BMI quintiles. Indeed, the highest BMI quintile had the lowest risk of airflow obstruction of any severity."

"One possible reason for the increased prevalence of asthma diagnosis among the obese might be related to the increased complaints of dyspnea and exercise limitations in this group.... [T]hese symptoms may explain why the obese are more likely to be treated with bronchodilators despite an absence of objective evidence for airflow obstruction. Such treatment has important clinical and therapeutic implications because there is a paucity of data supporting the use of bronchodilators for dyspnea unrelated to OAD."

"The mechanisms of dyspnea in obesity remain controversial. Obesity has been shown to adversely affect respiratory mechanics and gas exchange, decrease respiratory muscle function and lung volumes, and increase the work of breathing. The well-known decrease in end-expiratory lung volume in obesity has the potential to cause expiratory flow limitation despite normal airway function. *F*low limitation at rest or during exercise is a cause for ventilatory constraint, which could mimic the symptoms observed in patients with OAD who are flow limited owing to decreased maximal flow. Moreover, obesity can also increase the risk for aspiration pneumonia, obstructive sleep apnea, and cardiac syndromes, all of which are known risk factors for dyspnea genesis."

"Several limitations of the study should be mentioned. *F*irst, due to the cross-sectional design of the survey, based on our data, there is some ambiguity regarding the direction of the described relationships."

"Second, as with all observational studies, there is possibility that some unmeasured variable might have confounded our results. However, we carefully controlled for the most important covariates such as age, sex, and race, making this possibility less likely. Third, since there was no prospective follow-up of these participants, the effect of increased diagnosis of asthma (in the absence of objective evidence for airflow obstruction) on patient outcomes and health service utilization remains unknown. *F*inally, airflow obstruction in subjects with asthma may vary with time and can be normalized by bronchodilator treatment; the absence of spirometric values before and after bronchodilator use is an important limitation of our study."

[7] **"Viral Induction of a Chronic Asthma Phenotype and Genetic Segregation from the Acute Response," M.J. Walter, J.D. Morton, N. Kajiwara, E. Agapov, and M.J. Holtzman, *The Journal of Clinical Investigation* 110(2): 165-175, 2002**

"[*F*]indings therefore raise the possibility that asthma not only resembles a persistent anti-viral response but may even be caused by such a response, and so provide the experimental link between paramyxoviral infection in infancy with subsequent asthma in childhood and perhaps adulthood."

"We reported previously that asthma is characterized by persistent activation of the bronchial epithelium in a pattern that is similar to one inducible by viral infection. These findings suggested that an abnormal response to virus might contribute to asthma pathogenesis, but it was also possible that the epithelial response was driven by other inflammatory stimuli. *F*or example, allergen inhalation might also lead to epithelial activation indirectly via Th cell cytokine production, and under some circumstances even this response may require Th1 cytokines that are more typical of anti-viral responses. In addition, the previous data focused on the acute immune response to virus and so could not fully account for the persistent changes in epithelial behavior that occur in a chronic disease such as

asthma. In that context, the present study offers the critical information that a single paramyxoviral infection has the capacity to cause not only the acute manifestations of the asthma phenotype but also results in long-lasting changes in airway behavior that are characteristic of asthma. In addition, we demonstrate that the acute and chronic responses can b genetically segregated, ... Thus, specific host defense genes participate in mediating the acute inflammatory but not necessarily the chronic remodeling response to viral infection. As discussed below, the present findings suggest overlap in the underlying mechanism for the paramyxoviral response in mice and the phenotype in asthma."

"In particular, the present study also addresses the role of persistent infection and cytokine bias in the development of the chronic asthma phenotype after viral infection.... Based on this model and others as well as studies of tissue from human subjects, it has been suggested that viral persistence may drive the asthma phenotype in children. It has also been suggested that diminished IFN-γ production and decreased exposure to immune agents that stimulate this response may underlie the rising incidence of childhood asthma. However, we show that acute and chronic postviral phenotypes develop in the same manner in IFN-γ-deficient mice of analogous age... .We also precisely determined the tissue levels of replicating virus and viral genome, and similar to other reports, found no evidence of chronic infection or persistence of defective virus.... The results suggest a hit-and-run hypothesis for the viral effect, i.e., transient infection causes permanent alteration in host cell behavior. This type of mechanism has been proposed for oncogenic DNA viruses, but has not been observed for nononcogenic riboviruses."

"[W]e note that the capacity to develop two postviral chronic phenotype, goblet cell hyperplasia and airway reactivity, can be separated in the host genetic background used in the present study.... The present findings therefore support a scheme in which replicating virus causes direct induction of epithelial immune-response gene expression, and this leads to inflammation and inflammation- dependent hyperreactivity in the first few weeks after infection. However, additional genetic analysis will be needed to determine how these chronic phenotype segregate in mice and in humans and to define the relevant genes for susceptibility at each timepoint."

"The present effects of viral infection are distinct from the more transient impact of antigen sensitization/exposure even after repeated challenges."

"Taken together, the present findings establish the capacity of a single paramyxoviral infection to permanently change epithelial behavior and airway reactivity in a pattern that is remarkably similar to one in asthma. The present results add to previous findings indicating that paramyxoviral infection and asthma may activate a network of epithelial immune response. Thus, we now find that paramyxoviral infection may also lead to chronically abnormal airway structure and function, with goblet cell hyperplasia and airway hyperreactivity that is typical of asthma and other hypersecretory airway diseases. Furthermore, this chronic phenotype can be genetically segregated from the acute anti-viral response in mice. Several gene products appear to regulate goblet cell hyperplasia after allergen exposure, fitting a paradigm in which Th2 products (e.g., IL-4, IL-5, IL-9, and IL-13) may upregulate while Th1 products (e.g., IFN-γ) downregulate the response. Further studies will be required to precisely identify the genes responsible for epithelial remodeling and chronic hyperreactivity in response to paramyxoviral infection, but the lack of IFN-γ-dependent regulation in this setting implies that the viral pathway is distinct from pathways driven by allergen. Indeed, the present results raise the possibility that primary paramyxoviral infection in a specific genetic background may lead to chronic dysfunction of host cell behavior that overlaps with but does not depend on allergy."

RESPIRATORY DISEASES AND CONDITIONS – CHILDREN

[8] **"Identification of Population Subgroups of Children and Adolescents with High Asthma Prevalence: Findings from the Third National Health and Nutrition Examination Survey," M.A. Rodriguez, M.A. Winkleby, D. Ahn, and J. Sundquist, *Archives of Pediatric and Adolescent Medicine* 156(3): 269-275, 2002**

"Our study had the following 3 objectives: to provide national estimates of asthma prevalence in African-American, Mexican American and white (non-Latino) children and adolescents using several common definitions;

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to evaluate familial, sociodemographic, and environmental risk factors that are independently associated with current asthma in children; and to identify subgroups at particular risk for current asthma using 2 complementary data analytic approaches."

"For children with a parental history of asthma or hay fever, the likelihood of current asthma was 4 times greater than for children without a parental history of asthma or hay fever. Children with BMIs [body mass indexes] greater than or equal to the 85th percentile were 1.94 time more likely to have current asthma than children with BMIs less than or equal to the 85th percentile. Significant interactions were noted between both African American and Mexican American ethnicity and age. African American and Mexican American children showed a consistent prevalence of current asthma across age, while white children showed an increase in prevalence with age. The overall estimated odds ratio for African American children compared with white children was 1.42 (95% CI, 1.05- 1.93)."

"In this national sample of children from the 3 largest ethnic groups in the United States, the prevalence of current doctor-diagnosed asthma was 6.7% (95% CI, 5.6-7.8). This estimate was substantially higher than the 3.6% found in NHANES II, 1976 to 1980, which used a similar definition for asthma. Our estimate was also higher than the 4.3% found in children younger than 17 years with asthma in the past year, noted in the 1988 National Health Interview Survey. This increase in asthma prevalence has been previously reported but the reason for this increase is unclear."

"The prevalence of asthma or respiratory illness varied by the definitions used.... The significantly higher rates of hospitalization for wheezing among African Americans may reflect their greater asthma severity and/or inadequate control of asthma.... Hospitalization rates for Mexican American children were higher than for whites but did not reach statistical significance. This latter finding is in contrast to a recent analysis of NHANES III that reported children from Spanish-speaking families were at high risk for receiving inadequate therapy."

"In addition to the higher prevalence of current asthma among older children and higher hospitalization rates for wheezing in African American children, we found significant higher asthma prevalence in children with obesity."

"The findings in this study of a strong independent association of obesity with asthma in children and adolescents is cause for concern given the increases in obesity among children and adolescents."

"The mechanism underlying this relationship between obesity and asthma is unclear. It is possible that asthma may predispose young children to inactivity and this in turn may promote weight gain. Another possible mechanism examined in previous studies is that obesity may contribute to increased bronchial hyperreactivity. It is also possible that obese children with asthma are diagnosed more frequently than non-obese children with asthma.... Additionally, since both asthma and obesity can be seen as developmental disorders, a common underlying mechanism could be considered as well.... Understanding the relationship between obesity and asthma is an important area for future research, particularly given recent evidence that weight reduction in obese patients with asthma has been associated with improvements of lung function and other indicators of health status."

"In this study, there was a lack of significant association between asthma and SES, sex, and passive smoking.... [W]hile passive smoking has been noted to be a risk factor for asthma in young children, other studies have found that the effects of environmental tobacco exposure may vary with age."

"Children and adolescents with a parental history of asthma or hay fever comprised the groups with the highest prevalences of asthma. Children with a family history of asthma who were 10 years or older and who had BMIs greater than or equal to the 85th percentile had the highest prevalence of asthma. While they were the smallest group, almost 1 of every 3 currently had asthma. In general, the groups most likely to have asthma were also the groups to have the most severe cases of asthma. With or without family history, African American children had 2-fold greater rate of hospitalization for wheezing than Mexican American and white children."

"The results of this national study suggest a strong association among asthma, parental history of asthma, and obesity. Additional studies are needed to determine whether tailored intervention can minimize the negative effects of asthma."

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OTHER CANCER

[9] **"Environmental Toxins and Breast Cancer on Long Island. I. Polycyclic Aromatic Hydrocarbon DNA Adducts," M.D. Gammon, R.M. Santella, A.L. Neugut, S.M. Eng, S.L. Teitelbaum, A. Paykin, B. Levin, M.B. Terry, T.L. Young, L.W. Wang, Q. Wang, J.A. Britton, M.S. Wolff, S.D. Stellman, M. Hatch, G.C. Kabat, R. Senie, G. Garbowski, C. Maffeo, P. Montalvan, G. Berkowitz, M. Kemeny, M. Citron, F. Schnabel, A. Schuss, S. Hajdu, and V. Vinceguerra, *Cancer Epidemiology, Biomarkers & Prevention* 11: 677-685, 2002**

"The study reported here is based on data collected as part of the Long Island Breast Cancer Study Project, a large population-based case-control investigation that was motivated by community concerns for the effects of the environment on breast cancer risk. With blood samples obtained form newly diagnosed breast cancer cases and population-based controls, PAH [polycyclic aromatic hydrocarbons]-DNA adducts in mononuclear cells were measured using a competitive ELISA method, which is a more feasible laboratory approach in a large-scale epidemiological study than methods used in previous reports. An additional goal was to explore whether the association between adduct levels and breast cancer risk varied by cigarette smoking or grilled and smoked food consumption, which are among the primary sources of PAH exposure for U.S. residents."

"Among those with the highest quintile of exposure, as compared with the lowest quintile, the age- adjusted OR was 1.51 (95% CI, 1.04-2.20).... Because of the large number of women for whom no detectable levels of adducts were observed, we estimated the risk associated with having detectable adduct levels (age adjusted OR, 1.32; 95% CI, 1.00-1.74, for detectable *versus* nondetectable levels). Repeating the analyses with the sample restricted to those subjects with detectable levels of adducts, which can be interpreted as an indicator of the dose-response among the exposed, the ORs showed little or no increasing risk with increasing adduct formation; for the highest quintile of five categories as compared with the lowest, the OR was 1.13 (95% CI, 0.71- 1.81). There was no substantial confounding of the association between PAH-DNA adduct levels and breast cancer."

"The carcinogenicity of PAH, such as DMBA, on the mammary gland of laboratory animals has been well demonstrated, but their role in breast cancer development in women has not been well studied. PAH are bulky carcinogens, and elevated levels of PAH-DNA adducts have been observed in lung cancer cases. Furthermore, patterns of p53 mutation seen in the breast resemble those seen in the lung. Thus, it is possible that PAHs are breast carcinogens in humans as they are in animal models. In contrast, it is also possible that PAH may have antiestrogenic potential, as has been postulated for cigarette smoking, which is one of the major sources of PAH exposure in American populations. However, it is also unclear whether cigarette smoking has carcinogenic effects or antiestrogeic effects on the breast. Because of the biological plausibility of dual effects of PAH on the breast, utilization of a biomarker, such as DNA adducts, that reflects internal dose may help to clarify the issue."

"This study is the first large-scale epidemiologic study to evaluate whether DNA damage associated with PAH exposure increases the risk of breast cancer. In this population-based, case-control study among women on Long Island, a modest 50% elevation in the risk of breast cancer was noted in relation to the highest quintile of PAH-DNA adduct levels; however, no dose-response effect was observed. These results, coupled with the observed 50% increase in risk noted among women with detectable adducts, suggests that there may be a threshold effect. Results were not strongly confounded by known or suspected risk factors for breast cancer."

"Mean PAH-DNA adduct levels among control women did not vary with active or passive cigarette smoking status or within levels of grilled or smoked food consumption, which are reported to be among the largest sources of PAH among Americans. This lack of an association between adduct levels and the major sources of PAH adducts suggest perhaps that the adducts are better indicators of the body's response to the carcinogenic insult, rather than an indicator of exposure level. In other words, the presence of high levels of PAH-DNA adducts may be indicative of a susceptible individual."

"We also found elevated risks for breast cancer in relation to adduct levels associated with ER-PR- tumors as well as ER+PR+ tumors, but not for those with discordant receptor status.... [O]ur observation of an increase risk with PAH among concordant ERPR status tumors, regardless of whether the status of the receptor was positive or negative,

is not entirely consistent with other reports. However, our observation for an approximately 50% elevation in breast cancer risk associated with DNA adducts is consistent with two previously reported epidemiological studies."

"In conclusion, consistent with animal evidence that demonstrates the mammary carcinogenicity of PAH compounds, in this population-based study of women on Long Island an approximately 50% increase in breast cancer was noted in relation to PAH-DNA adducts, which are indicative of recent DNA damage. Our results are also consistent with two previous smaller epidemiological studies, which noted higher levels of adducts among breast cancer cases as compared with hospital-based controls. No trend in risk was observed, which is suggestive of a threshold effect. We did not observe a relation between PAH-DNA adduct levels and several sources of PAH, including cigarette smoking or intake of grilled and smoked foods, which is in contrast to several previous small investigations. However, these findings may suggest that individual differences in the response to similar levels of PAH exposure may be more relevant in breast carcinogenesis. PAH-DNA adducts reflect only recent exposures; therefore, future research in this area should focus on PAH exposure in the more distant past, which is likely to be more useful when assessing breast cancer risk. Biomarkers are not available that reflect exposures in the distant past, and other exposure assessment methods, such as geographic modeling, may need to be used when evaluating the breast carcinogenic potential in humans."

ETS EXPOSURE AND MONITORING

[10] "Prevalence of Exposure to Environmental Tobacco Smoke at Work and at Home – 15-year Trends in Finland," P. Jousilahti, and S. Helakorpi, *Scandinavian Journal of Work, Environment & Health* 28(2): 16-20, 2002

"In this paper we present the 15-year trends of exposure to environmental tobacco smoke at work and at home in Finland. In addition, changes in smoking arrangements in workplaces during the past 5 years are presented."

"During the 15-year period of this study, exposure to environmental tobacco smoke decreased markedly in Finland. Among nonsmokers, the exposure at work decreased to one-third between 1985 and 2000. Exposure at work was about three times more common among smokers than among nonsmokers, but a decreasing trend was seen among them. Exposure at home decreased only slightly. In 2000, about 14% of the nonsmoking men and 13% of the nonsmoking women were still exposed to environmental tobacco smoke either at the workplace or at home, or at both places."

"Both the generally decreasing smoking prevalence and legislative actions have contributed to the observed decrease in exposure to environmental tobacco smoke. Since the 1960s, the smoking prevalence of Finnish men has decreased by half, from about 60% to about 30%. A drastic decrease was observed already in the 1960s and 1970s, but a slower decrease has continued also since then. However, during the same time period, smoking among women increased somewhat. In our sample, 31.9% of the men and 14.3% of the women were daily smokers in 1985 as compared with 27.3% and 20.3% in 2000."

"The Tobacco Control act of 1976 created a basis for a smoke-free environment in Finland. The act prohibited smoking in most public places and public transportation vehicles.... In 1994 the act was amended to include workplaces as well. In 2000, it was expanded further to include also restaurants. In 2001, at least half of the area of a restaurant should be completely smoke-free."

"In 2000, no one was smoking inside in one-third of workplaces, in half of the workplaces smoking was permitted only in a separate smoking room, and in 7% it was also permitted in private rooms. However, in 7.3% of the workplace, smoking was permitted also in common areas.... In addition to bars and restaurants, workers are exposed to environmental tobacco smoke also in a small proportion of other workplaces, in which smoking in common areas has been prohibited since 1995. These workplaces are usually small companies with 2-10 workers."

"Recent results of the European Community Respiratory Health Survey show a very large variation between countries with respect to exposure to environmental tobacco smoke at work.... [O]ur results show that, in comparison to circumstances at the international level, exposure to environmental tobacco smoke at work in Finland is relatively rare."

[11] **"Exposure to Environmental Tobacco Smoke in Finland in 2000," T.P. Kauppinen, and S.V. Virtanen, *Scandinavian Journal of Work, Environment & Health* 28(2): 7-15, 2002**

"Finland restricted smoking at work in 1995 by passing the Tobacco Control Act, according to which indoor smoking at workplaces is prohibited except in smoking rooms isolated from other premises.... An amendment to the Tobacco Control Act restricted smoking of customers by requiring that 30% of customer seats be smokeless from March 2000 on. As of July 2001 this restriction applied to 50% of customer seats. Because smoking in restaurants is not entirely prohibited, a question rose about the criterion of smokelessness and the possible need for an exposure limit in smoky premises. The Finnish Social Affairs and Health asked the Scientific Committee on Health Effects of Chemicals to evaluate the health risks of environmental tobacco smoke in the current exposure situation. The exposure assessment in our paper was prepared in this context to support the quantification of risks due to environmental tobacco smoke."

"Approximately 330 000 - 340 000 salaried workers were exposed to environmental tobacco smoke at work in 1997 according to figures calculated from data of Statistics Finland. This is about 18% of 1.85 million employees and 16% of 2.17 million employed workers (including self-employed and family workers) in 1997.... The corresponding estimate in 1990 was over 600 000 exposed workers (32% of employees), indicating that the regulations restricting smoking at work in 1995 had decreased exposure significantly. The decrease was especially pronounced among those who were previously almost continually exposed."

"[W]e estimated 10 ug/m^3 to be representatives of the mean level of nicotine in Finnish restaurants in January 2000."

"The mean nicotine concentration was about 3 ug/m^3 in industrial and service workplaces and below 1ug/m^3 in office buildings."

"The overall mean level of all occupationally exposed persons was about 1 ug/m^3.... The lowest personal mean exposures are probably below 0.1 ug/m^3 (occasional exposure to almost smokeless air) and the highest ones exceed 100 ug/m^3 (continuous exposure in very smoky restaurants, etc.)."

"The exposure of the adult population to environmental tobacco smoke has been estimated on the basis of data from the National Public Health Institute in 1999.... According to these estimates about 440 000 adults aged 15-64 years (13%) were exposed to environmental tobacco smoke. The adult population may be exposed both at home and at work. Additional exposure during visits in smoky restaurants and other leisure-time activities is also possible."

"The number of children and adolescents under 15 years of age who are exposed to environmental tobacco smoke at home is 60 000-70 000, based on the prevalence figure of 7% from a Nordic study. Of this number, 20 000-30 000 are children under 5 years of age. Because somebody is smoking in 26% of Finnish homes, smoking in homes with children is rarer than in other households. Home is usually the only source of exposure among children. For young people approaching the age of 15 years, leisure-time activities (eg, smoking of friends) may also contribute to exposure."

"About 60 000-70 000 senior citizens, over 65 years of age, were exposed to environmental tobacco smoke mainly due to smoking of their spouses. According to the survey of the National Public Health Institute in 1999, 8.5% of respondents had a spouse who smoked at home. The predominant source of exposure among senior citizens is home, but also friends, restaurant visits, and other leisure-time activities may contribute."

"Because the levels of exposure to environmental tobacco smoke in smokers' homes have not been measured in Finland, we used measurements carried out in other countries to estimate that it would currently average 4 ug/m^3 for nicotine in units which are comparable with the estimates of occupational exposure."

"No direct data on the numbers of Finns exposed to environmental tobacco smoke outside work and home were available.... The number of Finns who spend leisure time in restaurants at least occasionally is very large, probably over 1 million."

"Although the prevalence of exposure to environmental tobacco smoke has decreased due to legal restrictions on smoking, it is still probably the most frequent occupational exposure to a chemical carcinogen."

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